OIPE JC
FEB 09 2005
PATENT & TRADEMARK OFFICE

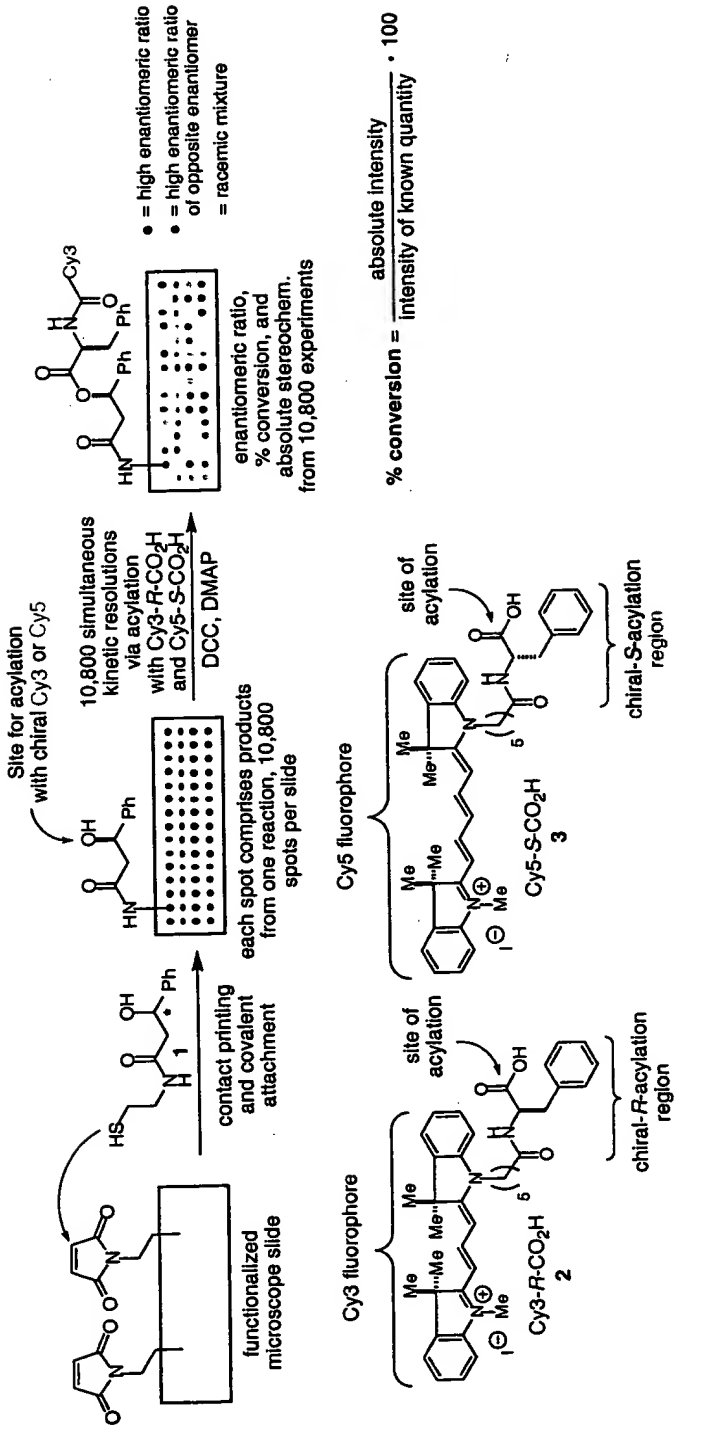


FIGURE 1

BEST AVAILABLE COPY

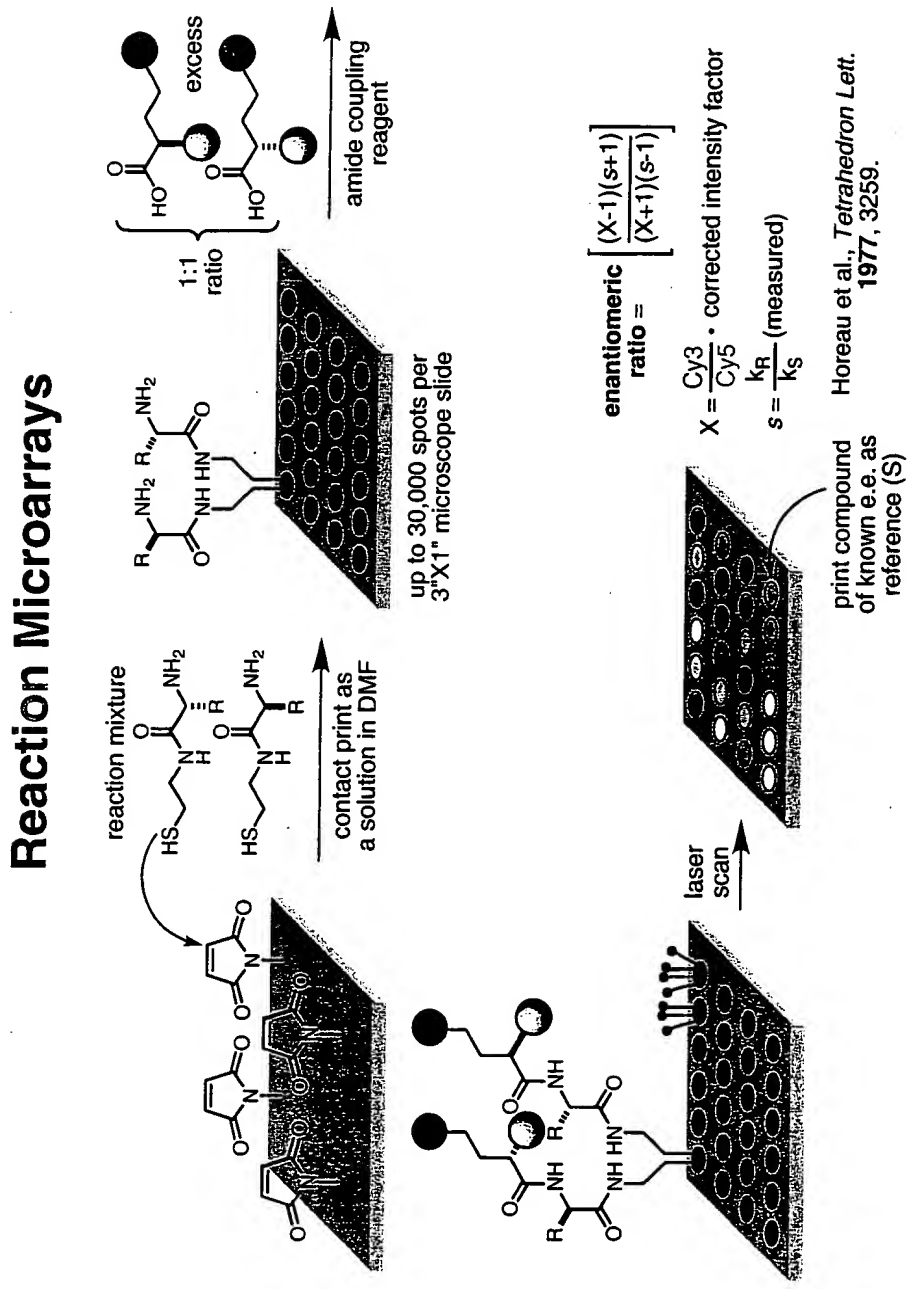

Reaction Microarrays
reaction mixture
contact print as a solution in DMF
up to 30,000 spots per 3"X1" microscope slide
1:1 ratio
excess
amide coupling reagent
laser scan
print compound of known e.e. as reference (S)
enantiomeric ratio = [(X-1)(s+1)/(X+1)(s-1)]
X = Cy3/Cy5 • corrected intensity factor
s = kR/kS (measured)
Horeau et al., Tetrahedron Lett. 1977, 3259.

FIGURE 2

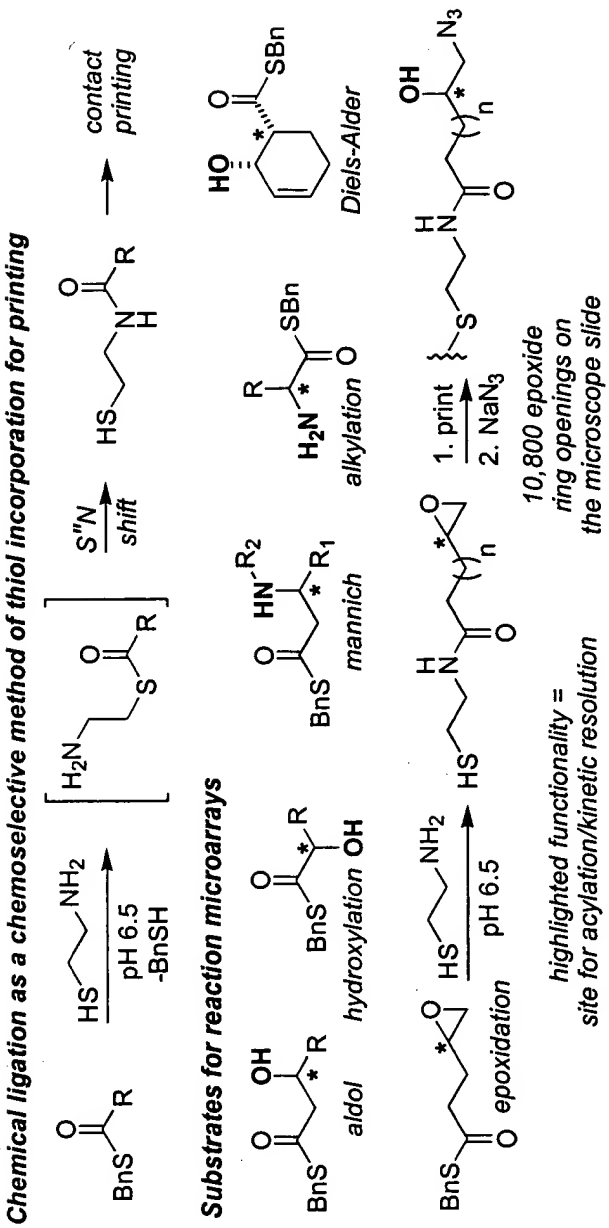
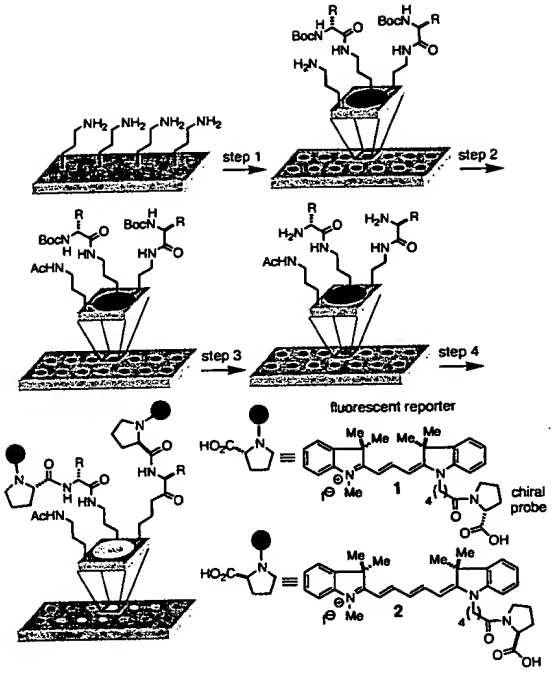

Chemical ligation as a chemoselective method of thiol incorporation for printing
pH 6.5
-BnSH
S"N
shift
contact
printing
Substrates for reaction microarrays
aldol
hydroxylation
mannich
alkylation
Diels-Alder
epoxidation
pH 6.5
1. print
2. NaN3
highlighted functionality =
site for acylation/kinetic resolution
10,800 epoxide
ring openings on
the microscope slide

FIGURE 3



Reagents and conditions: step 1) $BocHNCH(R)CO_2H$, PyAOP, $^iPr_2Net$, DMF,; step 2) Ac_2O, pyridine; step 3) 10% CF_3CO_2H and 10% Et_3SiH in CH_2Cl_2, then 3% Et_3N in CH_2Cl_2; step 4) Pentafluorophenyl diphenylphosphinate, $^iPr_2NEt$, 1:1 mixture of **1** and **2**, DMF, -20°C.

FIGURE 4

Attachment of amino acids as their allyl amides to selenyl bromide-functionalized microslides

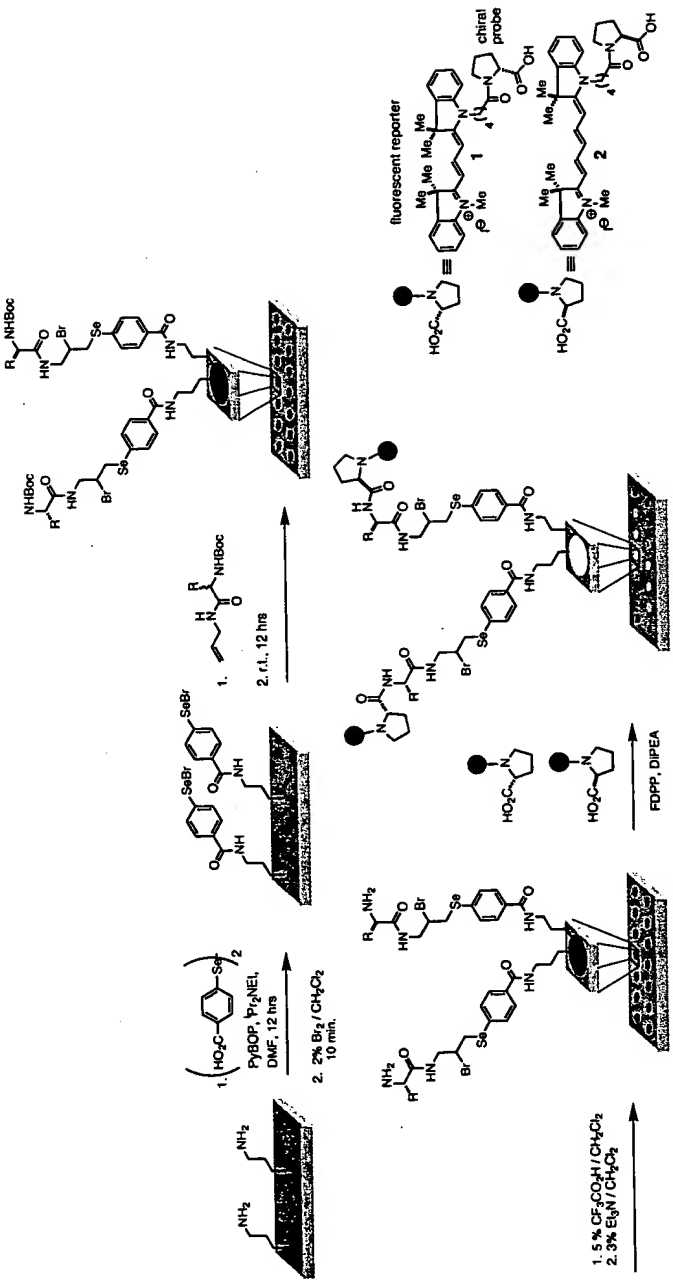


FIGURE 5

Attachment of amino acids as their allyl amides to nitrone-functionalized microslides

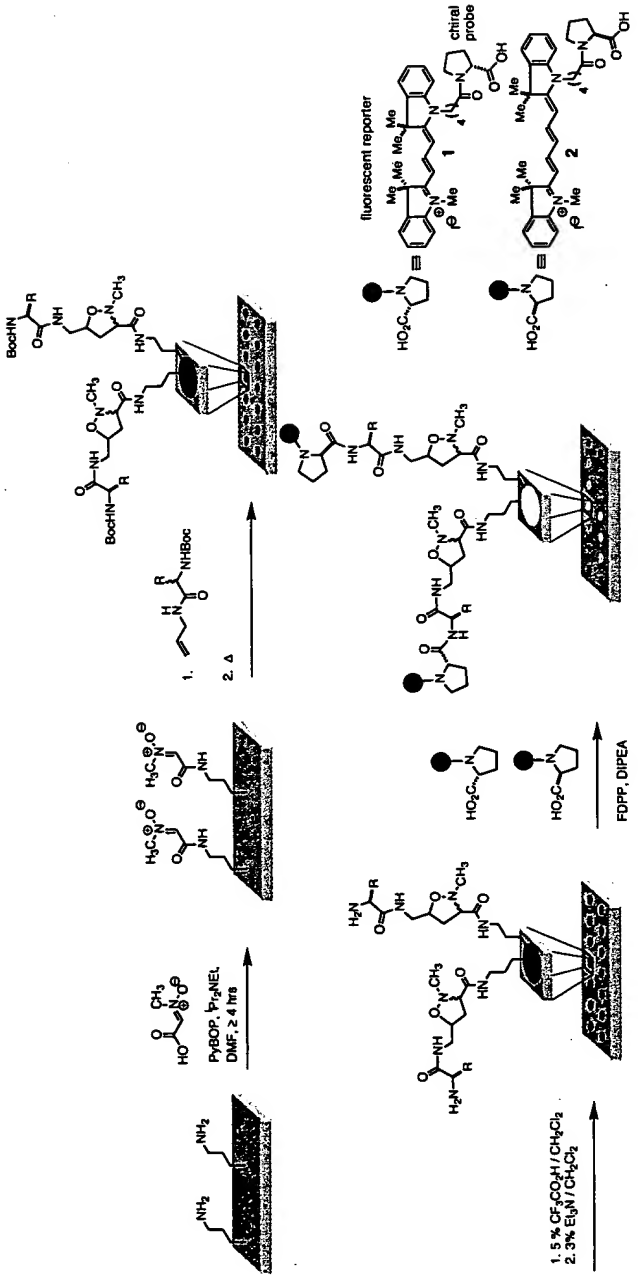


FIGURE 6

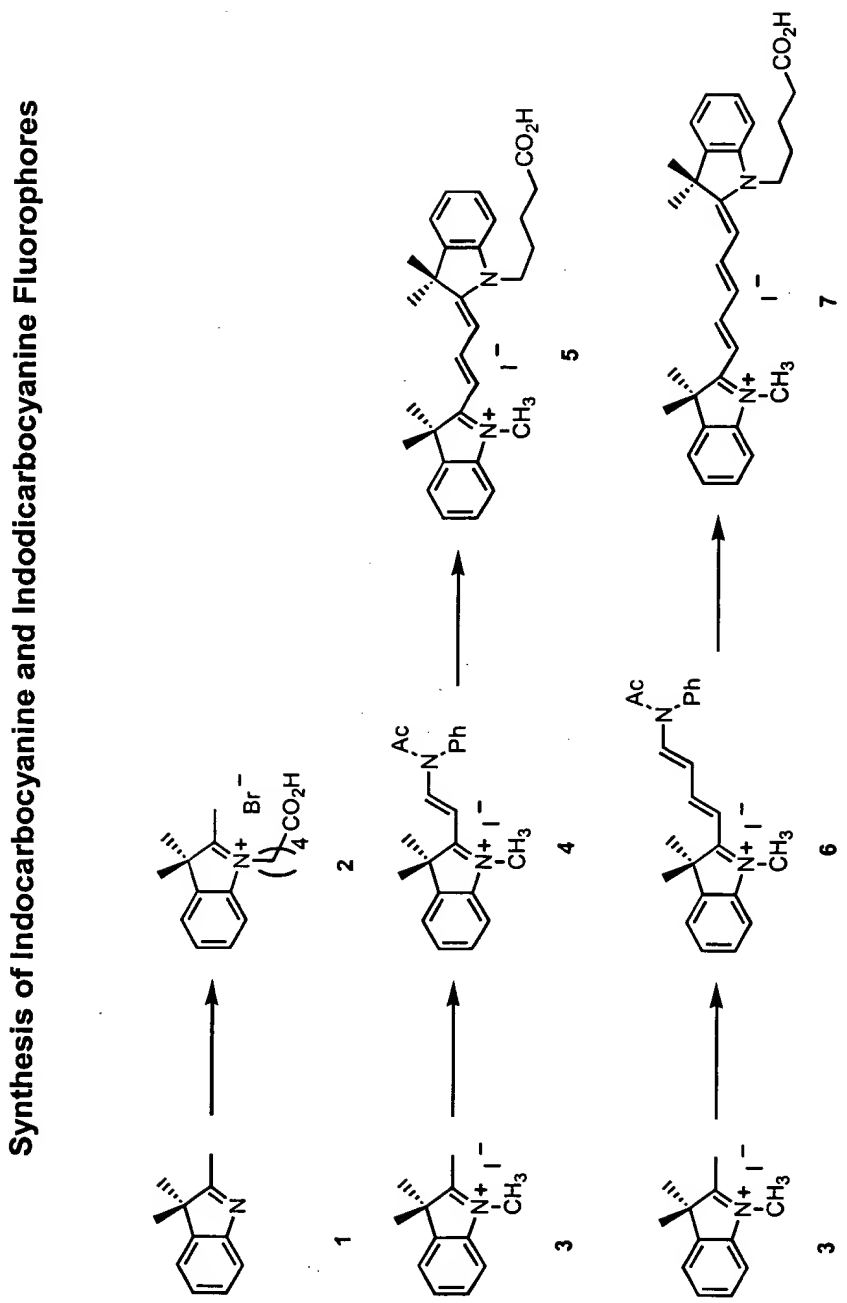

Synthesis of Indocarbocyanine and Indodicarbocyanine Fluorophores
1
2
3
4
5
6
7
3

FIGURE 7

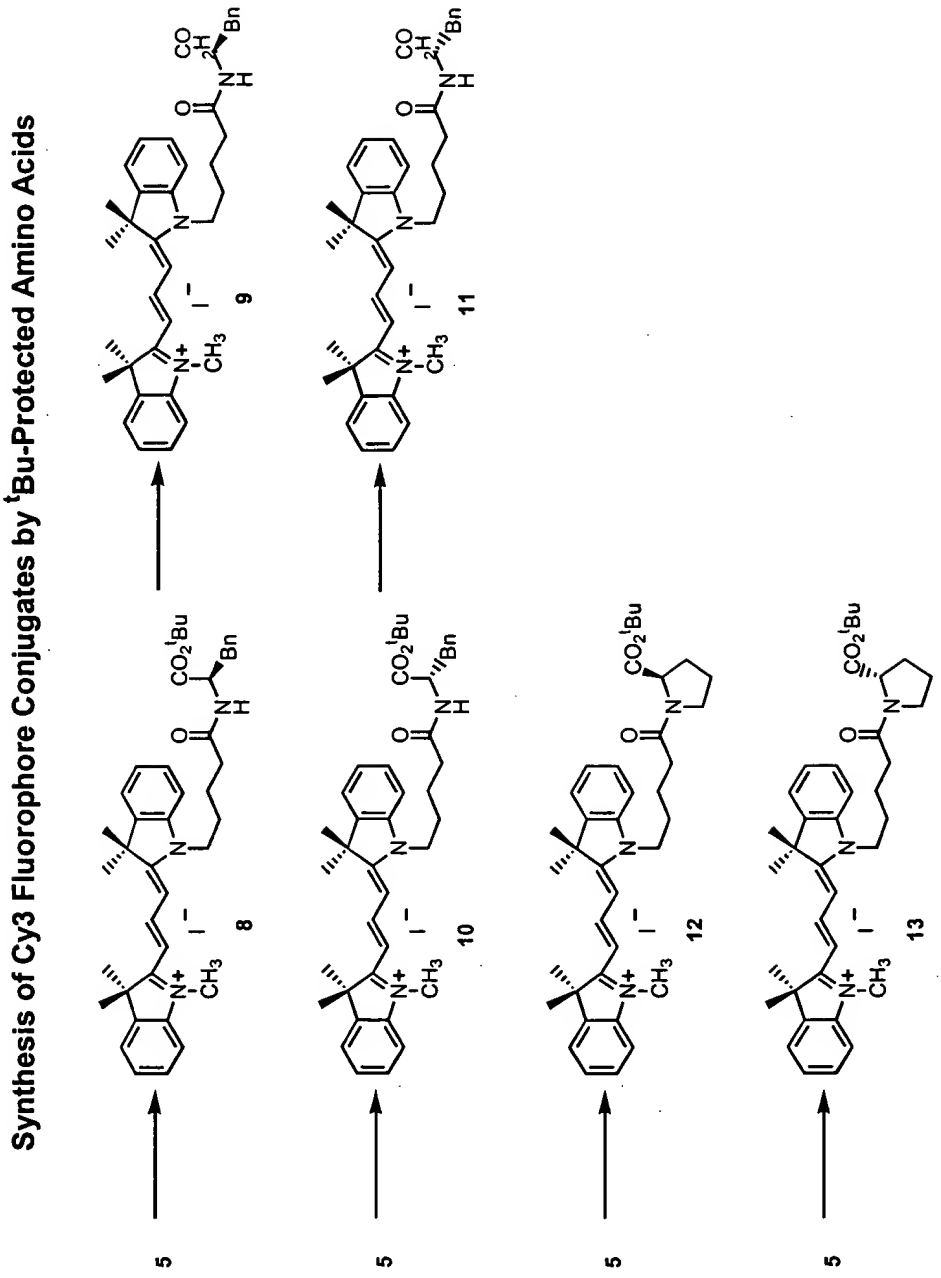

Synthesis of Cy3 Fluorophore Conjugates by tBu-Protected Amino Acids
5
8
9
10
11
12
13

FIGURE 8

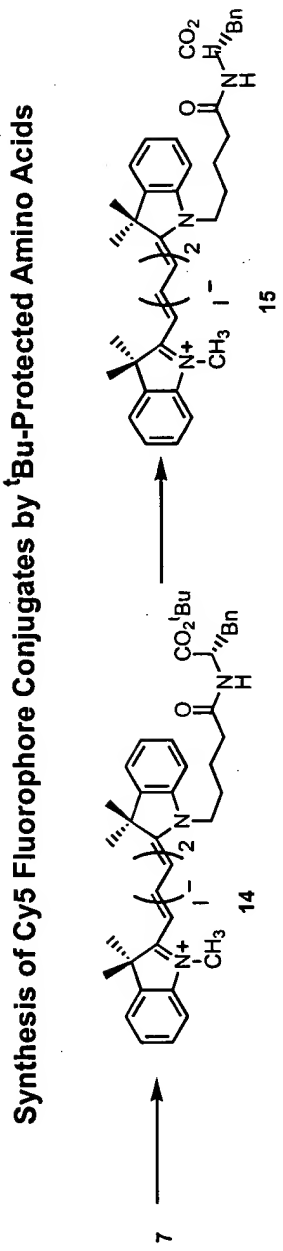

Synthesis of Cy5 Fluorophore Conjugates by tBu-Protected Amino Acids
7
14
15

FIGURE 9

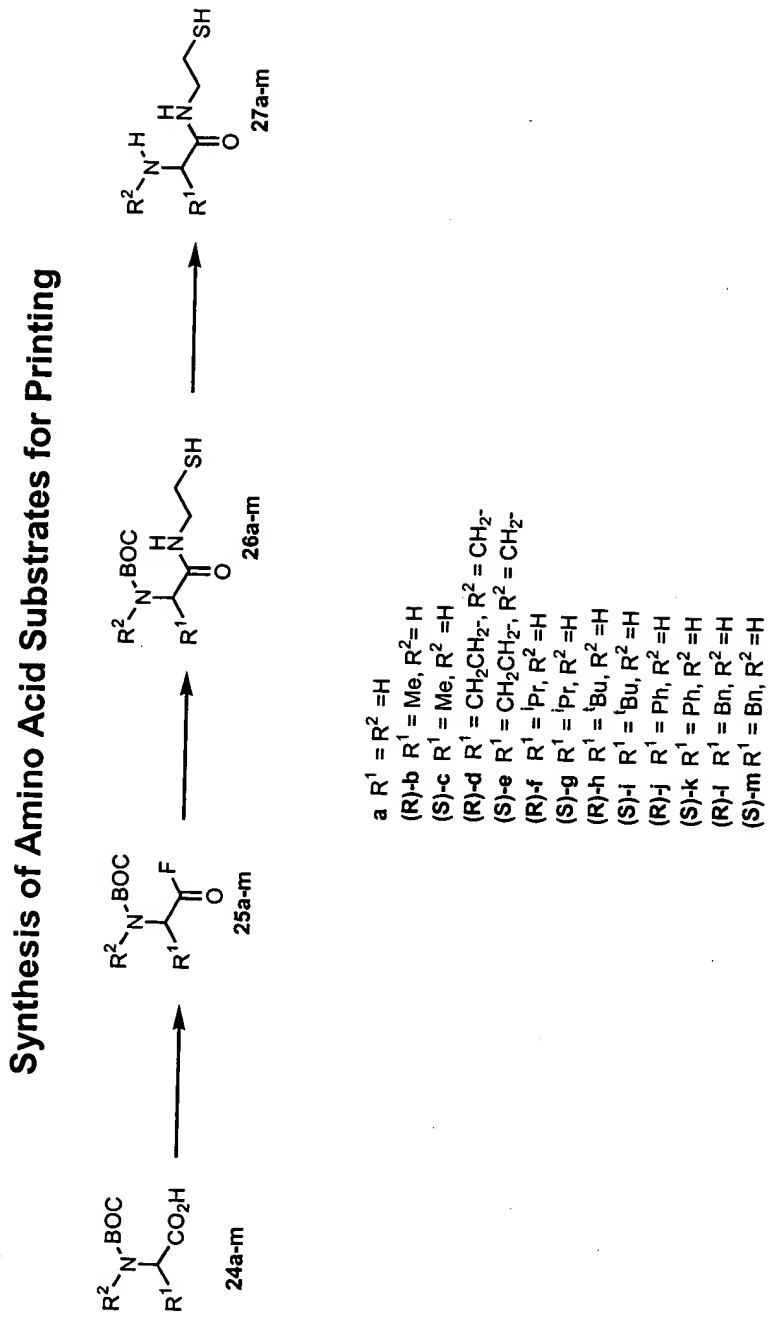

Synthesis of Amino Acid Substrates for Printing
24a-m
25a-m
26a-m
27a-m
a R1 = R2 =H
(R)-b R1 = Me, R2= H
(S)-c R1 = Me, R2 =H
(R)-d R1 = CH2CH2-, R2 = CH2-
(S)-e R1 = CH2CH2-, R2 = CH2-
(R)-f R1 = iPr, R2 =H
(S)-g R1 = iPr, R2 =H
(R)-h R1 = tBu, R2 =H
(S)-i R1 = tBu, R2 =H
(R)-j R1 = Ph, R2 =H
(S)-k R1 = Ph, R2 =H
(R)-l R1 = Bn, R2 =H
(S)-m R1 = Bn, R2 =H

FIGURE 10

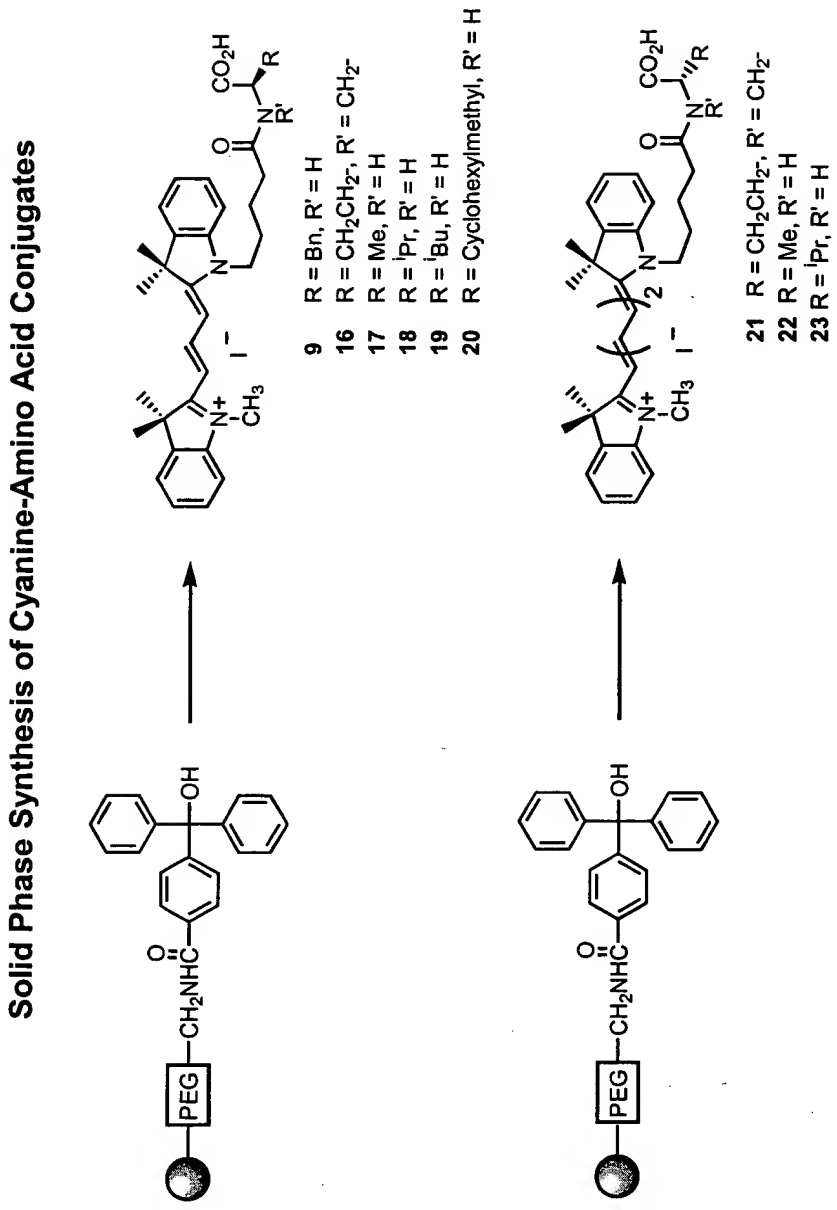
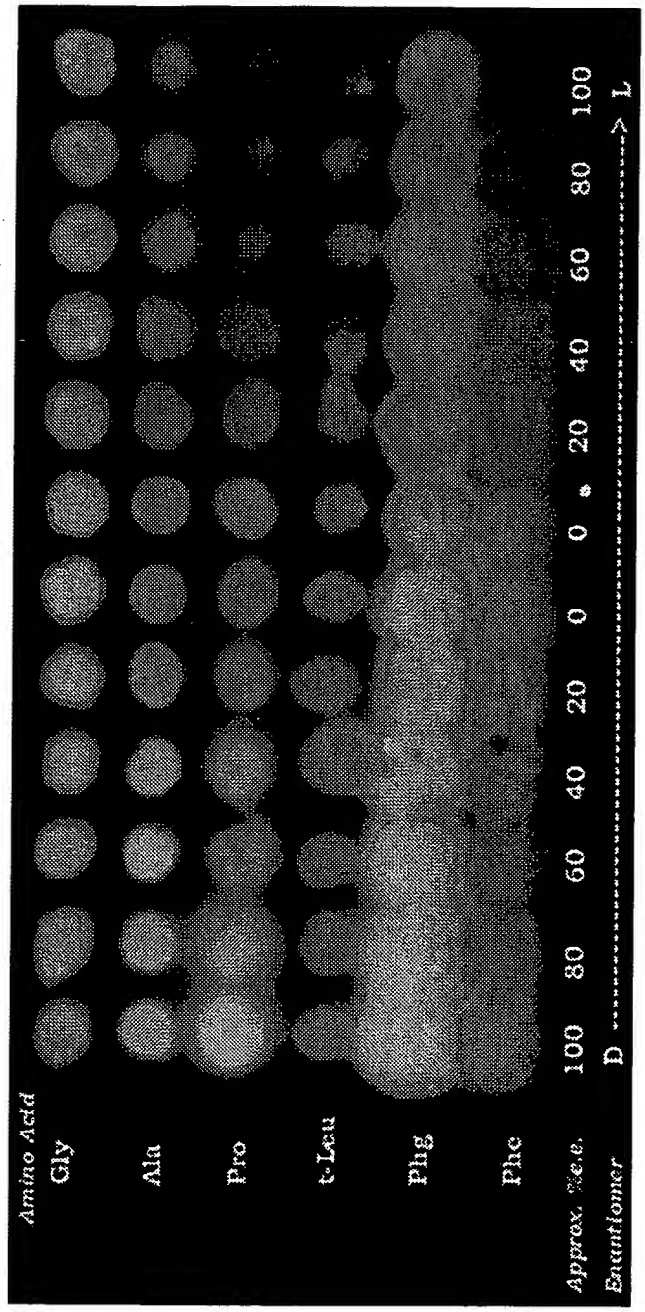
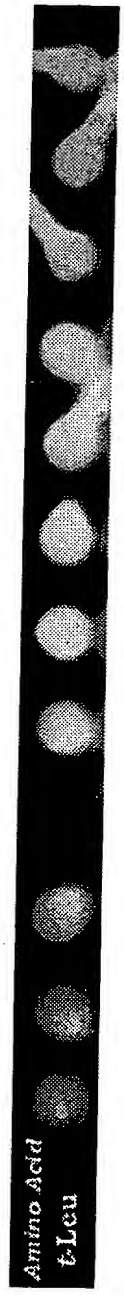

Solid Phase Synthesis of Cyanine-Amino Acid Conjugates
PEG
CH2NHC
O
OH
CO2H
N
R'
R
I−
CH3
9 R = Bn, R' = H
16 R = CH2CH2-, R' = CH2-
17 R = Me, R' = H
18 R = iPr, R' = H
19 R = iBu, R' = H
20 R = Cyclohexylmethyl, R' = H
21 R = CH2CH2-, R' = CH2-
22 R = Me, R' = H
23 R = iPr, R' = H

FIGURE 11



Ala (s = 2.0)													
Calculated %e.e	**100**	**87.5**	**60.4**	**39.7**	**21.5**	**7.4**	**13.4**	**5.2**	**25.1**	**49.3**	**71.0**	**100**	
Enantiomer	***D***	***D***	***D***	***D***	***D***	***D***	***D***	***L***	***L***	***L***	***L***	***L***	
Pro (s = 4.7)													
Calculated %e.e	**100**	**87.0**	**72.2**	**58.3**	**43.4**	**31.0**	**34.2**	**20.1**	**6.3**	**12.0**	**39.0**	**100**	
Enantiomer	***D***	***D***	***D***	***D***	***D***	***D***	***D***	***D***	***D***	***L***	***L***	***L***	
Phe (s = 1.8)													
Calculated %e.e	**100**	**85.0**	**61.5**	**39.6**	**18.4**	**0.7**	**10.4**	**3.4**	**30.6**	**53.3**	**81.9**	**100**	
Enantiomer	***D***	***D***	***D***	***D***	***D***	***D***	***D***	***L***	***L***	***L***	***L***	***L***	

FIGURE 12



t-Leu (s = 1.4)													
Approximate %e.e	100	80	60	40	20	0	0	20	40	60	80	100
Calculated %e.e	100	55.3	28.8	N/A	33.7	34.8	37.6	6.8	6.3	46.0	70.8	100
Expected enantiomer	*D*	*D*	*D*	*D*	*D*	*D*	*D*	*L*	*L*	*L*	*L*	*L*
Enantiomer	*D*	*D*	*D*	*N/A*	*D*	*D*	*D*	*D*	*L*	*L*	*L*	*L*

FIGURE 13

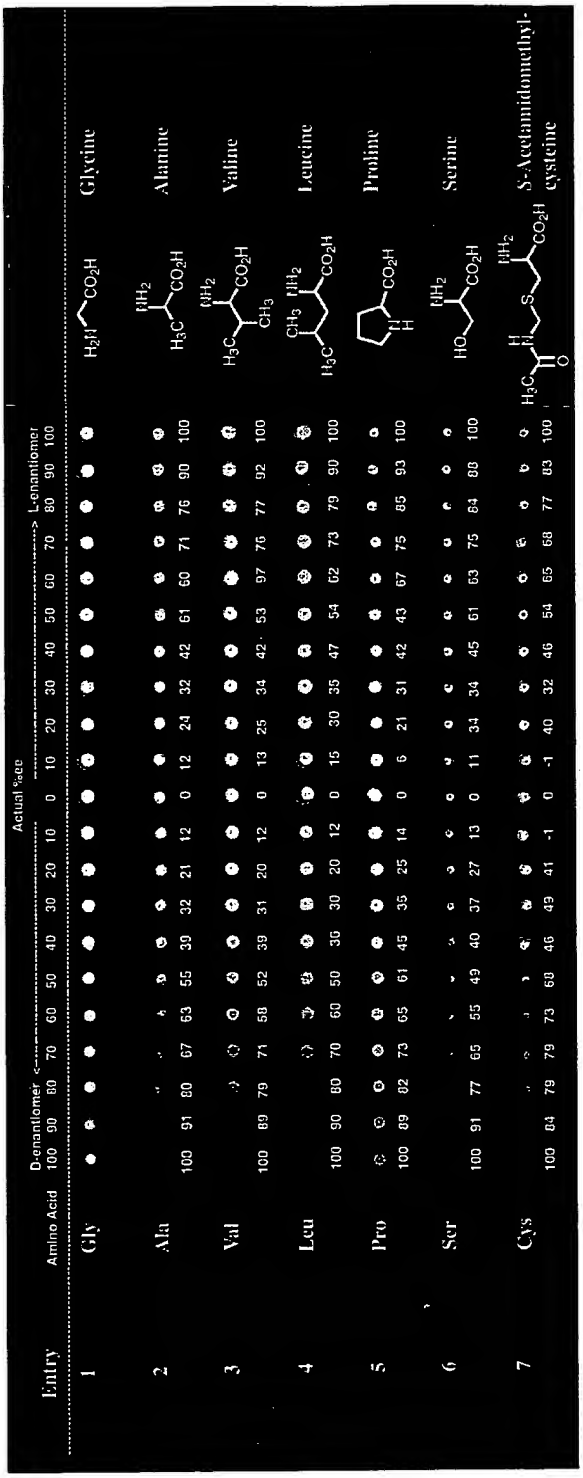

Actual %ee
D-enantiomer
L-enantiomer
Entry
Amino Acid
1 Gly Glycine
2 Ala Alanine
3 Val Valine
4 Leu Leucine
5 Pro Proline
6 Ser Serine
7 Cys S-Acetamidomethyl-cysteine

FIGURE 14

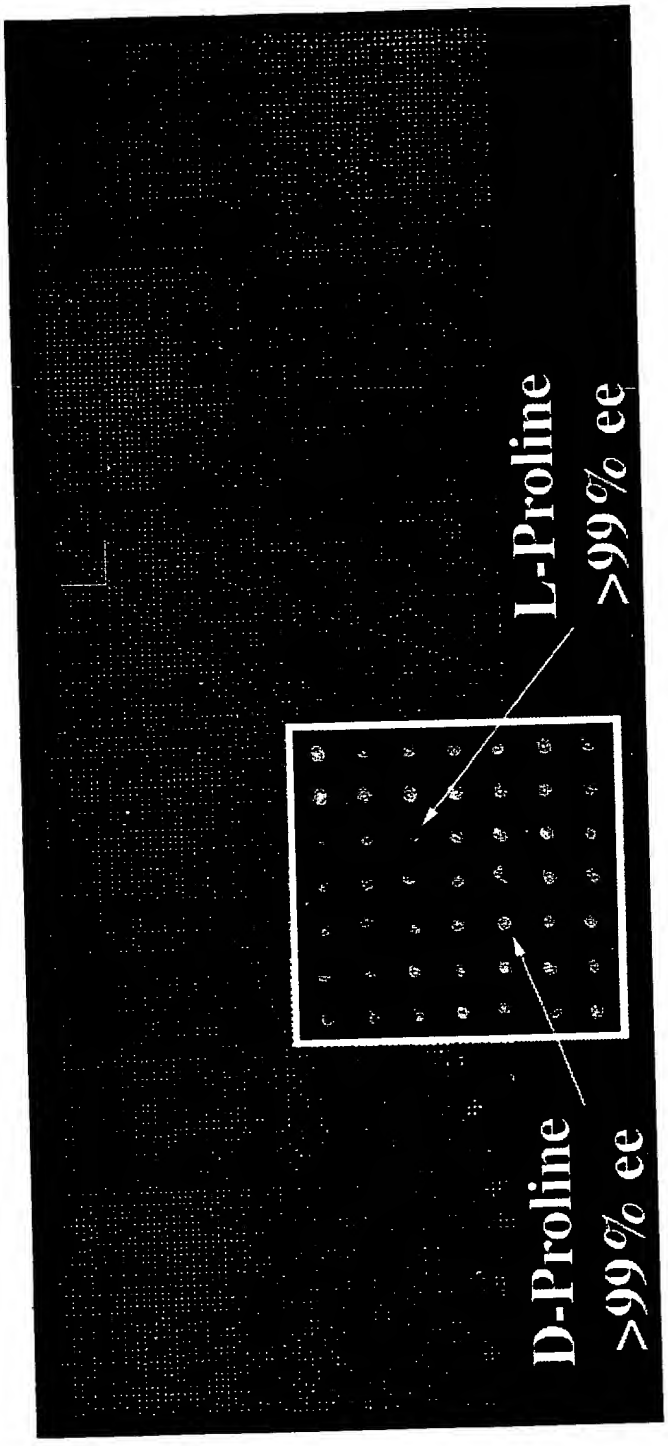


FIGURE 15

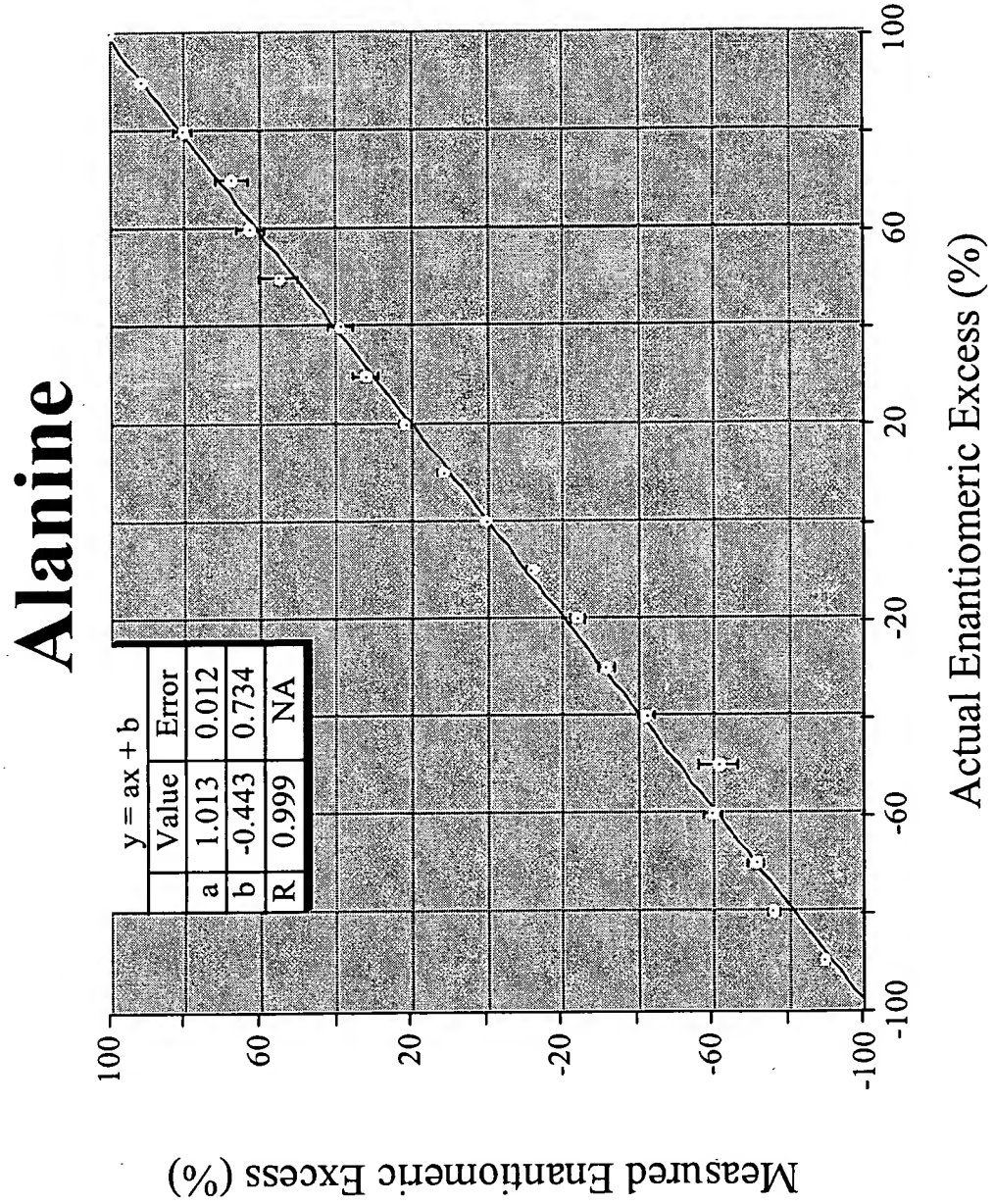

Alanine
y = ax + b
Value
Error
a
1.013
0.012
b
-0.443
0.734
R
0.999
NA
100
60
20
-20
-60
-100
Measured Enantiomeric Excess (%)
Actual Enantiomeric Excess (%)

FIGURE 16A

FIGURE 16B

Alanine	100% ee	90% ee	80% ee	70% ee	60% ee	50% ee	40% ee	30% ee	20 % ee	10% ee	0% ee
Valid cases	9.0	8.0	8.0	8.0	9.0	9.0	9.0	9.0	8.0	8.0	9.0
Mean	100.0	91.4	80.2	67.5	62.6	54.9	38.8	31.9	21.5	11.6	0.0
Std. error of mean	0.0	1.2	2.4	4.3	3.7	4.9	3.4	3.5	1.8	1.5	0.0
Variance	0.0	11.7	47.3	145.1	126.1	217.2	105.1	108.3	26.6	18.0	0.0
Std. Deviation	0.0	3.4	6.9	12.0	11.2	14.7	10.3	10.4	5.2	4.2	0.0
Minimum	100.0	86.5	69.7	47.7	48.0	35.9	26.5	21.4	14.4	6.0	0.0
Maximum	100.0	95.7	91.2	85.7	79.7	79.5	58.9	53.3	27.8	17.6	0.0
Range	0.0	9.2	21.5	38.0	31.7	43.6	32.3	31.9	13.4	11.6	0.0
Median	100.0	92.0	79.1	65.9	60.4	56.4	40.2	27.2	20.7	11.2	0.0
Geom. mean	100.0	91.3	79.9	66.5	61.8	53.1	37.7	30.6	21.0	10.9	—

Alanine	-10% ee	-20% ee	-30% ee	-40% ee	-50% ee	-60% ee	-70% ee	-80% ee	-90% ee	-100% ee
Valid cases	10.0	10.0	10.0	9.0	8.0	8.0	8.0	7.0	8.0	10.0
Mean	12.3	24.4	31.8	42.4	61.5	60.1	71.5	76.1	89.6	100.0
Std. error of mean	1.5	1.7	2.2	2.2	5.2	2.5	2.1	1.6	1.1	0.0
Variance	23.1	27.6	46.3	43.6	214.0	50.8	36.2	18.6	10.1	0.0
Std. Deviation	4.8	5.3	6.8	6.6	14.6	7.1	6.0	4.3	3.2	0.0
Minimum	5.1	14.4	19.7	29.8	44.5	47.1	64.4	67.1	85.8	100.0
Maximum	18.1	33.5	41.0	52.6	89.5	71.1	82.7	79.9	95.4	100.0
Range	13.0	19.1	21.3	22.8	45.0	24.0	18.3	12.8	9.6	0.0
Median	14.7	24.9	31.8	41.9	57.4	59.3	70.0	77.5	89.2	100.0
Geom. mean	11.2	23.9	31.1	41.9	60.1	59.7	71.2	76.0	89.6	100.0

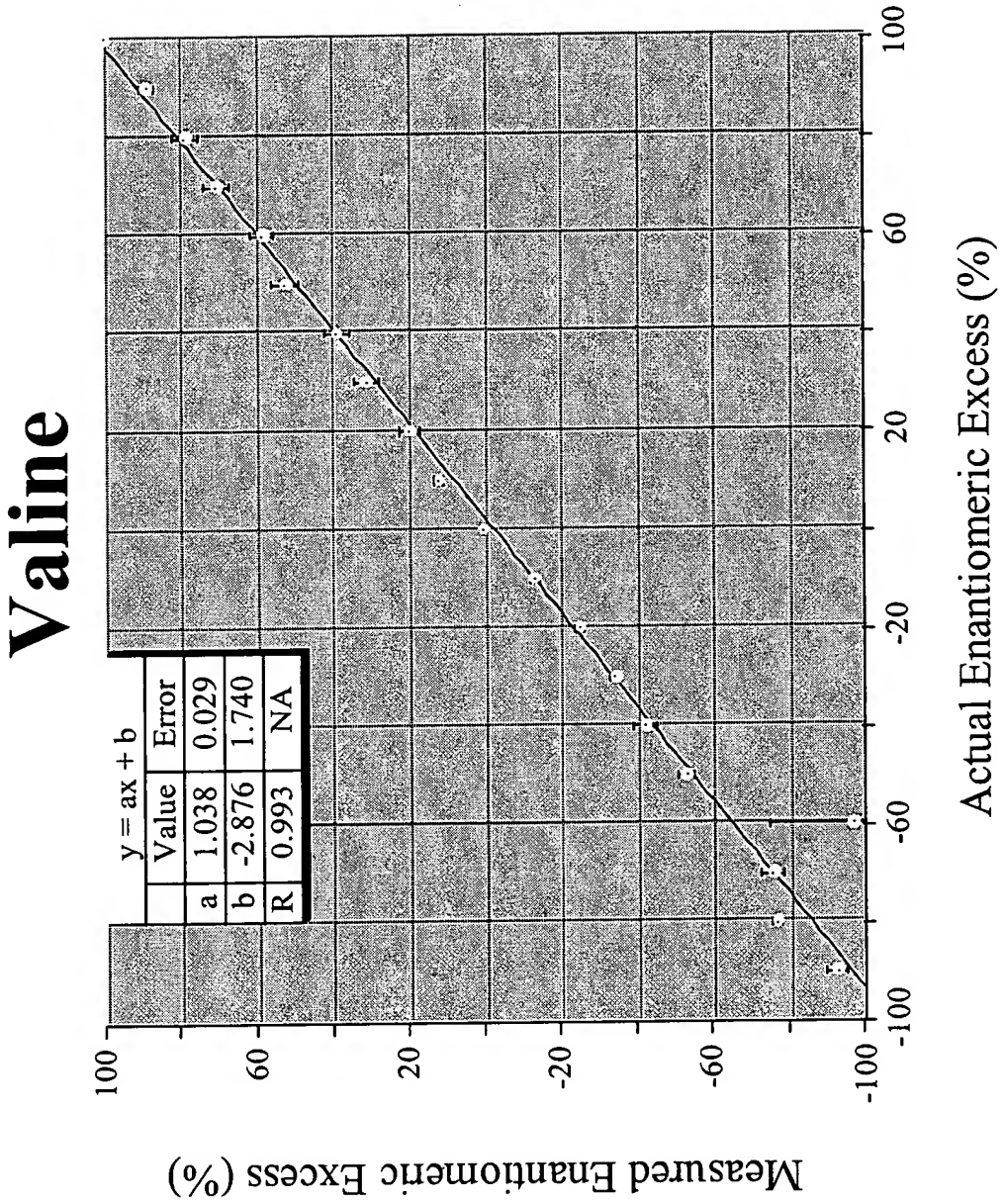

Valine
y = ax + b
Value
Error
a
1.038
0.029
b
-2.876
1.740
R
0.993
NA
100
60
20
-20
-60
-100
Measured Enantiomeric Excess (%)
100
60
20
-20
-60
-100
Actual Enantiomeric Excess (%)

FIGURE 17A

FIGURE 17B

Valine	100% ee	90% ee	80% ee	70% ee	60% ee	50% ee	40% ee	30% ee	20 % ee	10% ee	0% ee
Valid cases	7	7	6	7	7	7	7	7	7	7	10
Mean	100.0	88.8	78.8	70.7	58.4	52.1	38.9	31.1	19.6	11.9	0.0
Std. error of mean	0.0	2.0	3.2	3.5	3.3	3.7	3.4	3.0	2.8	1.3	0.0
Variance	0.0	28.3	60.8	84.4	74.4	94.2	79.1	64.5	55.4	12.0	0.0
Std. Deviation	0.0	5.3	7.8	9.2	8.6	9.7	8.9	8.0	7.4	3.5	0.0
Minimum	100.0	82.1	65.0	56.7	44.7	36.6	29.4	22.7	5.2	7.7	0.0
Maximum	100.0	98.0	84.9	82.6	68.5	66.1	52.6	41.2	28.5	16.7	0.0
Range	0.0	15.9	19.9	26.0	23.9	29.5	23.2	18.5	23.2	9.0	0.0
Median	100.0	88.0	80.9	72.7	58.5	51.2	35.8	26.3	19.4	11.4	0.0
Geom. mean	100.0	88.7	78.2	70.1	57.8	51.3	38.1	30.2	17.7	11.5	----

Valine	-10% ee	-20% ee	-30% ee	-40% ee	-50% ee	-60% ee	-70% ee	-80% ee	-90% ee	-100% ee
Valid cases	10	10	10	10	10	2	5	10	10	10
Mean	13.3	25.2	34.5	42.4	53.2	96.8	75.7	76.8	92.6	100.0
Std. error of mean	1.3	1.2	1.6	3.0	2.3	21.7	3.0	1.3	2.8	0.0
Variance	18.0	15.5	24.5	88.2	55.0	941.8	46.3	16.1	77.4	0.0
Std. Deviation	4.0	3.9	4.9	9.4	7.4	30.7	6.8	4.0	8.8	0.0
Minimum	7.8	19.2	27.3	34.0	45.7	75.1	71.3	69.8	81.6	100.0
Maximum	18.7	31.8	42.0	65.8	68.7	118.5	87.5	81.7	114.3	100.0
Range	10.9	12.6	14.8	31.8	22.9	43.4	16.2	11.9	32.6	0.0
Median	14.9	25.2	33.7	40.7	52.5	96.8	72.7	76.7	91.4	100.0
Geom. mean	12.7	24.9	34.1	41.7	52.7	94.4	75.5	76.7	92.2	100.0

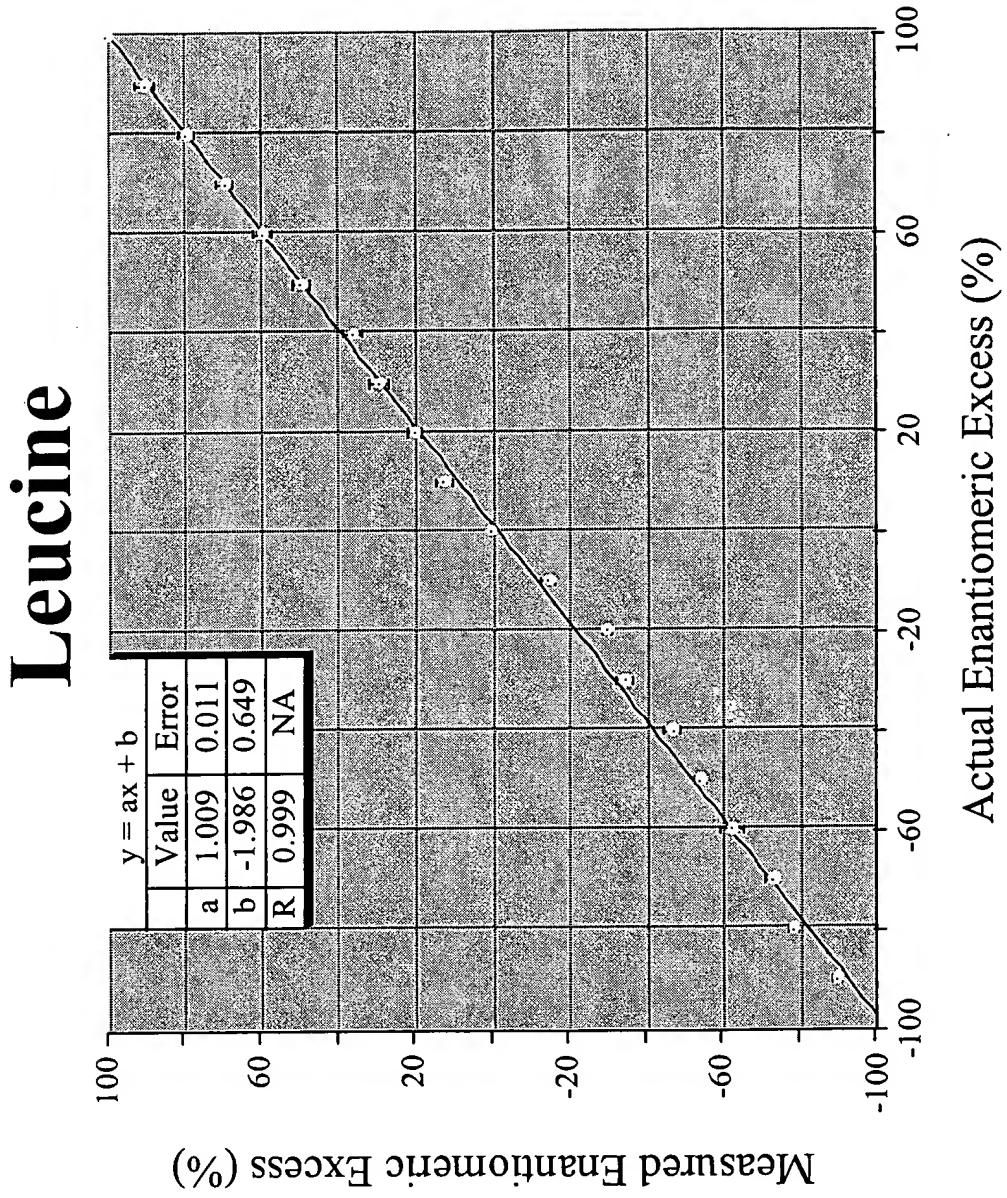

Leucine
y = ax + b
Value
Error
a
1.009
0.011
b
-1.986
0.649
R
0.999
NA
Measured Enantiomeric Excess (%)
Actual Enantiomeric Excess (%)
100
60
20
-20
-60
-100

FIGURE 18A

FIGURE 18B

Leucine	100% ee	90% ee	80% ee	70% ee	60% ee	50% ee	40% ee	30% ee	20 % ee	10% ee	0% ee
Valid cases	12	6	8	6	8	9	9	9	8	9	12
Mean	100.0	89.7	79.1	69.1	59.1	49.1	35.7	29.1	19.8	12.3	0.0
Std. error of mean	0.0	2.4	2.1	2.2	2.6	2.1	2.6	2.5	1.7	2.1	0.0
Variance	0.0	35.4	36.4	29.3	53.2	40.5	62.5	57.2	22.8	39.2	0.0
Std. Deviation	0.0	5.9	6.0	5.4	7.3	6.4	7.9	7.6	4.8	6.3	0.0
Minimum	100.0	81.1	69.3	62.5	46.7	39.5	23.1	20.1	13.2	-2.1	0.0
Maximum	100.0	95.5	87.1	76.1	68.1	58.5	47.3	44.2	28.3	17.4	0.0
Range	0.0	14.3	17.8	13.6	21.4	19.0	24.1	24.1	15.1	19.5	0.0
Median	100.0	91.6	78.8	69.6	61.9	51.6	37.3	28.4	20.1	14.9	0.0
Geom. mean	100.0	89.5	78.9	68.9	58.7	48.7	34.8	28.2	19.3	----	----

Leucine	-10% ee	-20% ee	-30% ee	-40% ee	-50% ee	-60% ee	-70% ee	-80% ee	-90% ee	-100% ee
Valid cases	11	10	9	10	11	11	11	11	9	12
Mean	14.8	29.8	34.8	47.0	54.3	62.6	73.2	78.5	89.7	100.0
Std. error of mean	1.8	1.3	2.2	1.9	1.7	2.9	1.7	1.1	1.2	0.0
Variance	34.1	15.6	42.3	37.8	33.4	93.9	31.3	13.7	12.6	0.0
Std. Deviation	5.8	4.0	6.5	6.2	5.8	9.7	5.6	3.7	3.6	0.0
Minimum	9.0	22.1	27.5	35.1	46.2	51.7	65.6	73.7	84.1	100.0
Maximum	28.3	38.2	47.4	57.3	64.5	86.1	86.1	86.6	97.1	100.0
Range	19.3	16.1	19.9	22.2	18.3	34.4	20.5	12.9	12.9	0.0
Median	13.4	29.6	35.4	47.4	55.3	60.3	72.4	79.3	89.2	100.0
Geom. mean	14.0	29.6	34.3	46.7	54.0	62.0	73.0	78.4	89.6	100.0

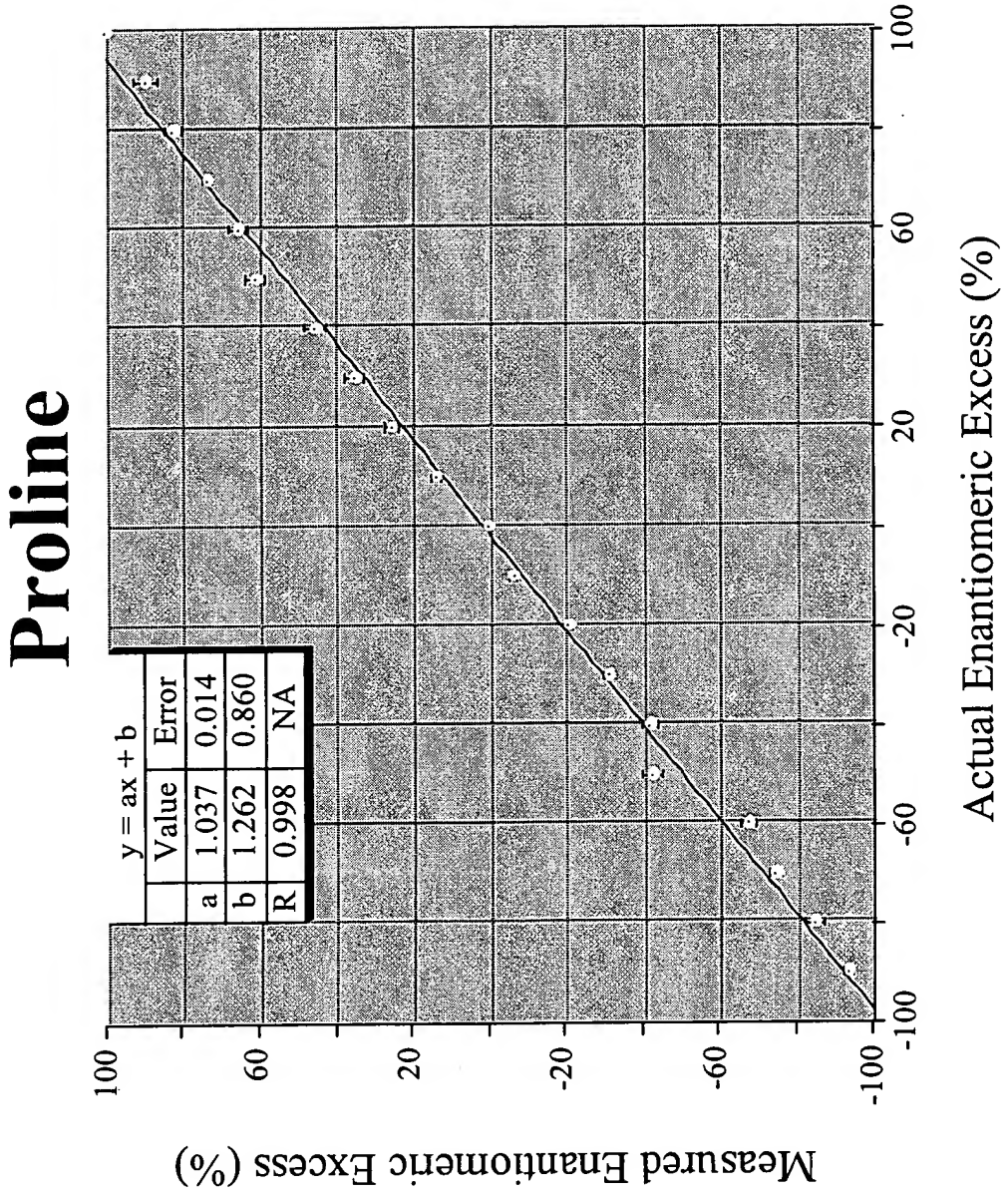

Proline
y = ax + b
Value
Error
a
1.037
0.014
b
1.262
0.860
R
0.998
NA
Measured Enantiomeric Excess (%)
Actual Enantiomeric Excess (%)
100
60
20
-20
-60
-100

FIGURE 19A

FIGURE 19B

Prolin	100% ee	90% ee	80% ee	70% ee	60% ee	50% ee	40% ee	30% ee	20 % ee	10% ee	0% ee
Valid cases	5	4	5	5	5	4	4	5	5	5	3
Mean	100.0	89.4	82.2	73.3	65.2	60.8	45.3	34.9	25.2	13.6	0.0
Std. error of mean	0.0	3.1	2.2	1.1	2.3	2.5	2.8	2.4	2.0	1.4	0.0
Variance	0.0	38.0	23.8	6.3	26.3	24.6	31.4	27.7	20.4	9.9	0.0
Std. Deviation	0.0	6.2	4.9	2.5	5.1	5.0	5.6	5.3	4.5	3.2	0.0
Minimum	100.0	85.2	75.0	71.2	59.1	56.7	39.6	27.4	20.0	9.7	0.0
Maximum	100.0	98.3	88.2	77.4	73.2	66.6	52.1	40.8	30.1	18.1	0.0
Range	0.0	13.1	13.2	6.2	14.2	9.9	12.5	13.2	10.1	8.4	0.0
Median	100.0	87.1	82.5	72.9	64.9	60.0	44.8	34.4	23.1	12.7	0.0
Geom. mean	100.0	89.3	82.1	73.3	65.0	60.7	45.1	34.6	24.9	13.3	----

Prolin	-10% ee	-20% ee	-30% ee	-40% ee	-50% ee	-60% ee	-70% ee	-80% ee	-90% ee	-100% ee
Valid cases	9	10	9	10	9	10	10	10	8	10
Mean	6.4	21.1	31.2	42.1	42.6	67.5	74.6	84.6	93.3	100.0
Std. error of mean	1.1	0.9	1.0	2.0	3.0	2.0	1.5	2.3	1.3	0.0
Variance	11.4	8.5	8.9	38.5	81.4	40.7	23.0	52.2	12.6	0.0
Std. Deviation	3.4	2.9	3.0	6.2	9.0	6.4	4.8	7.2	3.5	0.0
Minimum	-1.7	16.2	26.3	32.6	22.0	57.6	64.2	68.8	88.9	100.0
Maximum	9.5	24.9	35.0	55.5	53.3	79.5	80.2	97.0	98.9	100.0
Range	11.2	8.8	8.7	22.9	31.4	21.9	16.0	28.3	10.1	0.0
Median	6.4	21.6	32.6	43.3	43.1	65.6	76.5	85.6	92.2	100.0
Geom. mean	----	20.9	31.1	41.7	41.6	67.3	74.5	84.3	93.3	100.0

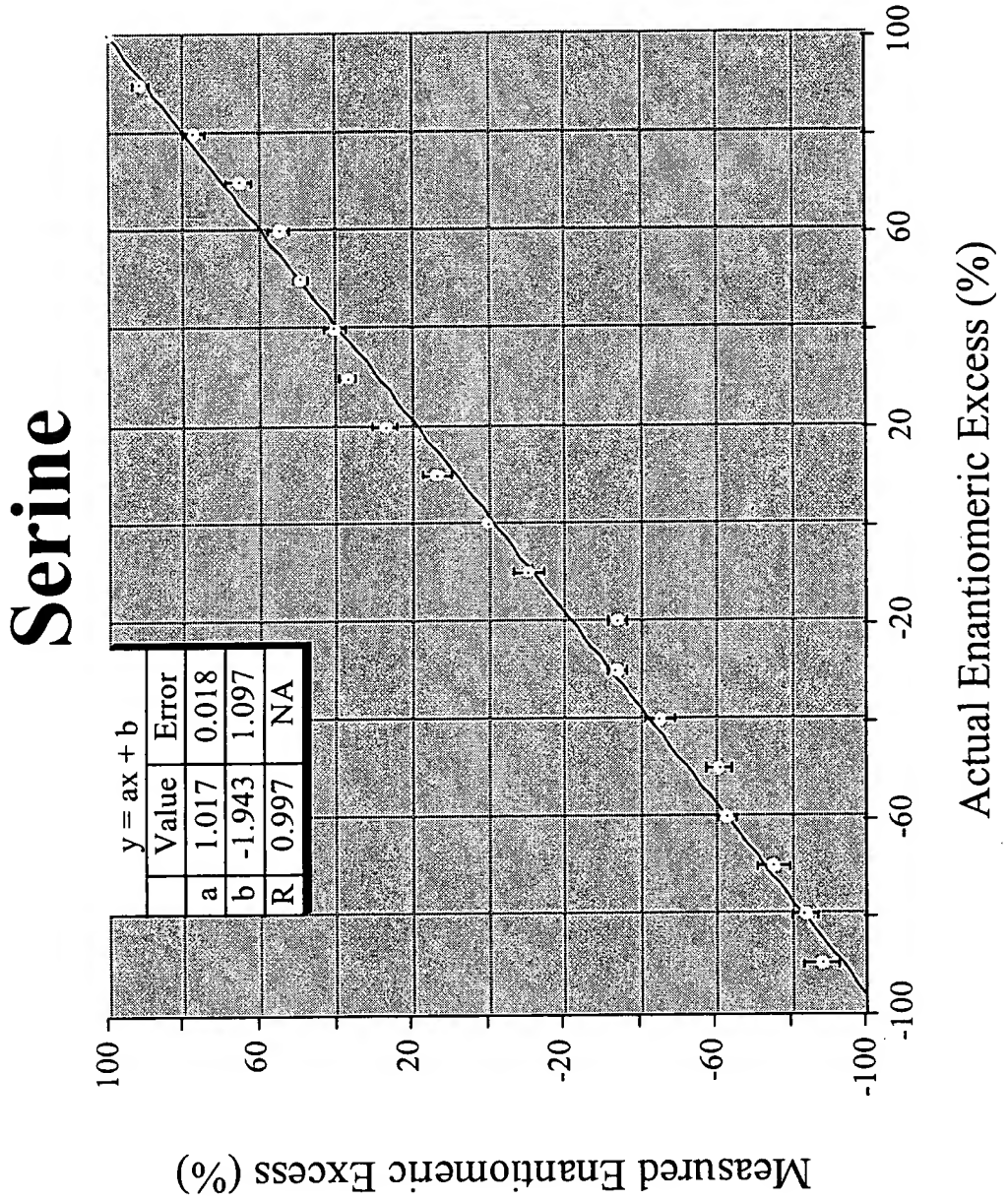

Serine
y = ax + b
Value
Error
a
1.017
0.018
b
-1.943
1.097
R
0.997
NA
100
60
20
-20
-60
-100
-100
-60
-20
20
60
100
Measured Enantiomeric Excess (%)
Actual Enantiomeric Excess (%)

FIGURE 20A

FIGURE 20B

Serine	100% ee	90% ee	80% ee	70% ee	60% ee	50% ee	40% ee	30% ee	20 % ee	10% ee	0% ee
Valid cases	6	6	6	6	5	6	5	6	6	6	8
Mean	100.0	91.1	77.1	65.0	54.7	46.9	40.0	36.8	27.0	13.4	0.0
Std. error of mean	0.0	2.2	2.8	3.3	2.6	1.7	2.6	2.2	3.5	3.5	0.0
Variance	0.0	28.5	47.6	63.5	34.7	17.2	35.0	29.8	73.0	72.4	0.0
Std. Deviation	0.0	5.3	6.9	8.0	5.9	4.1	5.9	5.5	8.5	8.5	0.0
Minimum	100.0	86.5	66.0	53.7	46.2	42.9	34.2	27.5	15.2	0.4	0.0
Maximum	100.0	98.4	85.6	77.0	62.6	54.7	46.7	44.2	39.5	26.6	0.0
Range	0.0	11.9	19.6	23.3	16.3	11.7	12.6	16.8	24.4	26.2	0.0
Median	100.0	88.7	77.9	65.0	54.5	49.4	37.6	37.7	26.7	13.2	0.0
Geom. mean	100.0	91.0	76.8	64.6	54.4	48.8	39.7	36.4	25.8	8.1	----

Serine	-10% ee	-20% ee	-30% ee	-40% ee	-50% ee	-60% ee	-70% ee	-80% ee	-90% ee	-100% ee
Valid cases	7	8	8	8	8	8	7	7	7	8
Mean	10.9	34.0	33.8	45.4	60.9	63.0	75.2	83.6	88.0	100.0
Std. error of mean	4.1	2.6	2.5	3.9	3.5	2.7	4.5	3.3	4.6	0.0
Variance	116.7	52.4	49.8	122.1	99.4	57.3	144.2	74.4	147.5	0.0
Std. Deviation	10.8	7.2	7.1	11.1	10.0	7.6	12.0	8.6	12.1	0.0
Minimum	-2.6	18.0	21.3	30.9	46.4	46.8	54.3	70.4	65.9	100.0
Maximum	26.4	41.7	43.2	60.2	76.4	70.4	91.8	96.3	101.8	100.0
Range	29.0	23.7	21.8	29.3	30.0	21.6	37.5	25.9	35.9	0.0
Median	11.2	36.6	34.8	47.1	62.3	66.4	76.2	83.9	87.8	100.0
Geom. mean	----	33.1	33.1	44.1	60.2	62.6	74.3	83.2	87.2	100.0

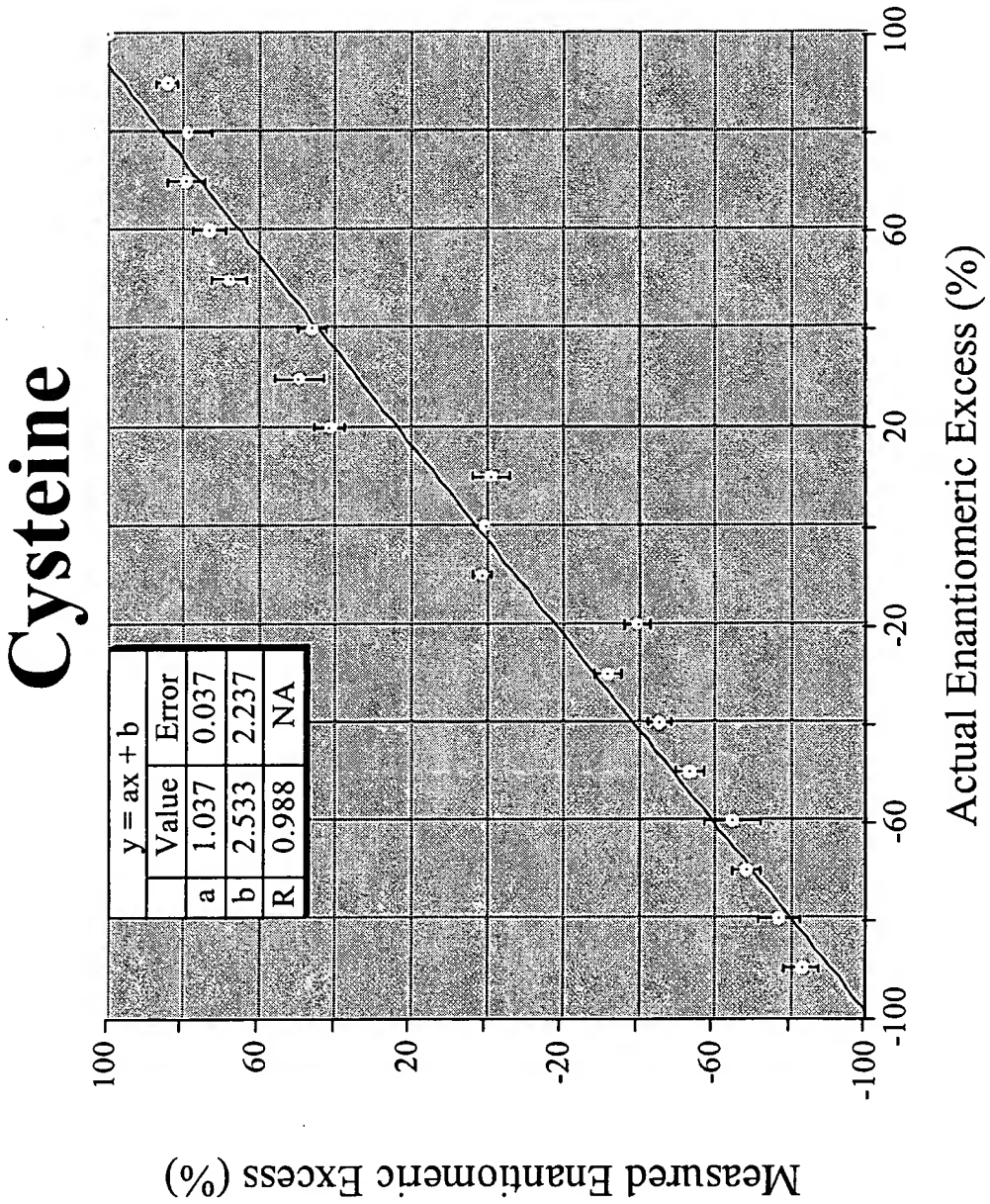

Cysteine
y = ax + b
Value
Error
a
1.037
0.037
b
2.533
2.237
R
0.988
NA
Measured Enantiomeric Excess (%)
Actual Enantiomeric Excess (%)
100
60
20
-20
-60
-100
-100
-60
-20
20
60
100

FIGURE 21A

FIGURE 21B

Cys	100% ee	90% ee	80% ee	70% ee	60% ee	50% ee	40% ee	30% ee	20 % ee	10% ee	0% ee
Valid cases	8	8	8	8	6	6	6	8	8	8	6
Mean	100.0	84.0	78.7	79.1	72.9	67.7	45.8	49.2	41.2	-1.5	0.0
Std. error of mean	0.0	2.8	6.6	5.0	4.1	4.8	3.5	6.2	4.1	5.1	0.0
Variance	0.0	63.8	351.6	196.9	100.7	172.0	73.6	307.7	134.1	209.5	0.0
Std. Deviation	0.0	8.0	18.8	14.0	10.0	13.1	8.6	17.5	11.6	14.5	0.0
Minimum	100.0	72.0	37.4	60.0	58.3	47.8	32.8	36.0	27.2	-33.3	0.0
Maximum	100.0	95.4	97.7	101.5	89.3	82.2	55.4	89.4	56.1	12.0	0.0
Range	0.0	23.4	60.3	41.5	31.0	34.4	22.6	53.5	28.9	45.3	0.0
Geom. mean	100.0	83.7	76.0	78.0	72.3	66.5	45.0	47.1	39.8	—	—

Cys	-10% ee	-20% ee	-30% ee	-40% ee	-50% ee	-60% ee	-70% ee	-80% ee	-90% ee	-100% ee
Valid cases	6	7	7	6	6	7	7	6	6	7
Mean	-1.0	40.0	32.3	45.7	53.7	64.6	68.4	77.1	83.1	100.0
Std. error of mean	2.4	3.3	3.6	3.3	3.5	7.3	3.9	5.3	4.6	0.0
Variance	34.7	76.6	88.4	67.3	73.4	373.1	105.3	171.7	125.8	0.0
Std. Deviation	5.9	8.8	9.4	8.2	8.6	19.3	10.3	13.1	11.2	0.0
Minimum	-8.4	25.0	19.3	34.1	39.3	44.7	49.7	55.0	63.0	100.0
Maximum	6.6	51.1	44.5	55.5	64.8	102.8	79.3	92.7	92.5	100.0
Range	15.0	26.0	25.2	21.5	25.6	58.0	29.6	37.7	29.5	0.0
Geom. mean	—	39.1	31.1	45.1	53.1	62.5	67.6	76.1	82.4	100.0

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